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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,600	09/15/1999	ALAN BERRY	3161-18-PUS	5327

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	

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05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/341,600	BERRY ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-72 and 74-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-72 and 74-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 40-72 and 74-91 are pending and under consideration in this Office Action.

2. The objection to 73 as being a substantial duplicate of claim 50 is moot in view of applicants' cancellation of claim 50 in the amendment dated 02/13/2007.

3. The rejection of claims 40-72 and 74-76 under 35 U.S.C. 112, second paragraph, as being indefinite has been withdrawn in view of the claim amendments in the amendment dated 02/13/2007.

4. The rejection of claims 40-72 and 74-76 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicants' amendment and arguments dated 02/13/2007.

5. Claims 82, 84, 89, and 87 are objected to under 37 CFR 1.75 as being a substantial duplicates of claim 72, 78, and 71, respectively.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 40-70, 72, 74-77, 80-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' arguments filed 02/13/2007 have been fully considered but they are not persuasive.

As stated in the previous Office Actions, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing the claimed modified coding region of a gene encoding glucosamine-6-phosphate synthase that has increased enzyme activity requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities, which would clearly constitute undue experimentation.

Guo et al. (Proc Natl Acad Sci U S A. 2004 Jun 22;101(25):9205-10; reference of record) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced.

Applying this estimate to the *E.coli* glucosamine-6-phosphate synthase having 100 mutation within its amino acid sequence consisting of 609 amino acid residues would result in about 9×10^{-20} % of random mutants having any activity. Similarly, 50 mutations only about 9×10^{-10} % would be active, and 25 mutations about 3×10^{-5} % would be active.

Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for an *E.coli* glucosamine-6-phosphate synthase having 25 mutations (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the case for an *E.coli* glucosamine-6-phosphate synthase having 50 mutations would not be possible.

The examiner maintains that since a large amount of screening is required, the specification and prior art must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided by the instant specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006. Furthermore, the specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006 do not disclose what domains and motifs within the amino acid sequence of the *E.coli* glucosamine-6-phosphate can be modified to make a glucosamine-6-pohsphate synthase that has increased activity compared to an unmodified glucosamine-6-pohsphate synthase.

The examiner maintains that general teachings for screening and searching for the glucosamine-6-phosphate synthase with the desired properties is not guidance for making the claimed invention. Without additional guidance regarding the specific type of genetic modification to perform on the specific codons within the coding region of any polynucleotide encoding glucosamine-6-phosphate synthase that lead to the desired increase in enzyme activity

or decreased product inhibition, then the experimentation left to those skilled in the art is undue. The examiner's position is that the instant specification is only enabling for a method for searching and screening for mutant glucosamine-6-phosphate synthases that have the recited properties such as increased enzyme activity and reduced product inhibition.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 40, 53, 55, 62-64, 71, 75, 76-79, and 87-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Dutka-Malen et al. Dutka-Malen et al. reference has been attached to the previous Office Action dated (7/20/00) and is not attached to the instant Office Action.

Dutka-Malen et al. make a genetically engineered E.coli host cell (see Fig. 1, p. 288) which is transformed with a recombinant vector containing the E.coli gene encoding glucosamine-6-phosphate synthase suitably linked to a lac promoter wherein said host cell overexpresses glucosamine-6-phosphate synthase as evident by an increase in enzyme activity. Glucosamine-6-phosphate synthase catalyzes the formation of glucosamine-6-phosphate. Genetic modifications include transformation of E.coli host cells with a recombinant vector containing a nucleic acid sequence which encodes glucosamine-6-phosphate synthase and overexpression of said synthase. Furthermore, linking the nucleic acid sequence encoding glucosamine-6-phosphate synthase to said lac promoter in said recombinant vector is a mutation to the glucosamine-6-phosphate synthase gene (glms). Dutka-Malen et al. teach a process comprising culturing the genetically engineered *E.coli* host cell in LB medium and the cells harvested by centrifugation and enzyme purification performed (see pp. 288-290).

Since the process steps taught by Dutka-Malen et al. are the same as the recited process steps, then the process would produce glucosamine and the harvesting of the cells by centrifugation would result in the recovery of the produced glucosamine in the remaining culture media. Thus, the reference teachings anticipated the claimed invention.

Conclusion

10. No claim is allowed.

11. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

TEKCHAND SAIDHA
PRIMARY EXAMINER